

REMARKS

In accordance with 37 C.F.R. § 1.121, a marked up copy of the presently amended specification and claims is appended hereto. Additions are noted by underlining. Deletions are noted by bracketing. Furthermore, to ensure that Applicants' pending claims match those of the Patent Office, a clean copy of the entire set of pending claims is also appended hereto. No new matter has been added as a result of these amendments. The Applicants have reviewed the specification and claims to correct typographical errors. The amendments reflect these corrections.

All of the above changes are cosmetic and none raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq.* The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

- having been altered in any way for any reason related to patentability;
- having been narrowed;
- a concession that the invention as patented does not reach as far as the original, unamended claim;
- a surrender of any subject matter as a condition of receiving a patent; and/or,
- estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen;

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

The Applicants again wish to thank the Examiner for his consideration during a telephonic interview conducted with the Applicants' representatives on November 20, 2002. During the interview, the Examiner requested that the Applicants summarize the contents of the interview. Although the Examiner has now provided an Interview Summary, the Applicants enclose a copy of the Interview Summary that they prepared at the Examiner's request.

Claims 1-18, 20-46, 48-153, 155-157, 165-166, and 171-173 are pending in this application. Claims 58-149, 161, 163-164, and 167-170 have been withdrawn from consideration by the Examiner, as being drawn to non-elected inventions. Claims 31, 35, and 173 have been amended. All of the remaining pending claims 1-18, 20-46, 48-57, 150-153, 155-157, 165-166, and 171-173 stand rejected.

The Applicants also submit the Declaration of Dr. Mark Erion, as discussed in the telephonic interview of November 20, 2002.

The Applicants note that in the Examiner's rejections in points 6, 7, 8, 11, and 12 of the Office Action dated July 15, 2002, the Examiner has rejected claim 154. However, claim 154 was cancelled in a previous response. The Applicants respectfully ask the Examiner to clarify these rejections.

I. THE ELECTION AND RESTRICTION REQUIREMENT

In the Advisory Action, the Examiner clarified that 58-149, 161, 163-164, and 167-170 have been withdrawn from consideration, as being drawn to non-elected inventions.

The Applicants have asked the Examiner to cancel claims 58-149, 161, 163-164, and 167-170 without prejudice. Therefore, Applicants believe that this response is complete.

II. THE 35 USC § 112, SECOND PARAGRAPH REJECTIONS

- B. Claims 1-3, 7, 9-18, 20-46, 48-53, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.**

This rejection is respectfully traversed.

The Examiner states:

The phrase in lines 16-17, page 128, "M is selected from...but is not an FBPase inhibitor" is indefinite. What do the Applicants intend by "biologically active agent? How active and active as what? Office Action
p. 6

The Examiner views the above rejection as related to the remaining rejection of claims 1-3, 7, 9-18, 20-46, 48-53, 150-157, and 165 and the new rejection of 166 and 171-173 for indefiniteness for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner states:

The phrase in lines 20-21, page 128 “M is not -NH(lower alkyl), -N(lower alkyl)₂” is indefinite. M-PO₃⁻² etc must be biologically active. Are ⁻²O₃P-NH(lower alkyl) or ⁻²O₃P-N(lower alkyl)₂ biologically active? If not, the proviso excluded something that is not present. Office Action pp. 6-7

As the Examiner has said that these two rejections are related, they will be traversed together. The Examiner notes that the Applicants have pointed to pp. 21-22 to clarify the nature of M. (Office Action p. 7). The Examiner says that “this passage implies that MPO₃⁻² etc must be the biologically active agent.” (Office Action p. 7). The Examiner then goes on to say:

The radical M itself might contain phosphorus but it would be a second phosphorus atom. The compound M-H might or might not be biologically active. However, we do not know if only therapeutic activity is indented [sic]. Are poisons and biochemical intermediates also covered by the term? Office Action p. 7

The Examiner further states that he searched the US patent files and the Internet for the terms “group”, “attached”, “PO₃⁻²”, and “biologically active agent.” (Office Action p. 7). The Examiner says that he can find no evidence that it is an art recognized phrase. (Office Action p. 7).

The Examiner feels that “the proviso concerning amines only clouds the issue.” (Office Action p. 7). The Examiner states:

The Examiner understand what radicals are excluded and that it was done to avoid art. Applicants’ uncertainty about the amine exclusion only means that they also are uncertain as to the metes and bounds of the structure M if they are uncertain about the biological activity of ⁻²O₃P-NH(lower alkyl). Office Action pp. 7-8

The Applicants note that they too conducted a search of the Internet. This non-comprehensive search turned up numerous sites with the term “biologically active agent,” including those advertising textbooks and those selling chemicals. Copies of some of these are enclosed for the Examiner’s convenience. They are from the Websites of the Research Foundation of the State University of New York Technology Transfer Office, MDL Information Systems, Cornell University, cplbookshop.com, chipsbooks.com, weyrich.com, immunepro.com, amazon.com, and agnic.org. The term “biologically active” has been highlighted. In addition, a recent search of patents issued from 1996-2002 revealed that 1,538 patents used the term “biologically active” in the claims. A similar search revealed that 197

patents used the term “biologically active agent” in the claims. The Applicants respectfully assert that “biologically active agent” is an art recognized phrase.

The Applicants also conducted a non-comprehensive search of the Internet (not the USPTO site) using the terms “group”, “attached”, and “biologically active agent.” This search resulted in multiple listings including US Patent No. 6,005,004.

Furthermore, the Examiner recognizes the specification at pp. 21-22 defines “biologically active drug or agent” as:

The term “biologically active drug or agent” refers to the chemical entity that produces the biological effect. In this invention, biologically active agents refers to $M-PO_3^{2-}$, $M-P(O)(NHR)^{6-}$, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ where M can be the same M as in the parent drug or a metabolite. pp. 21-22

According to MPEP § 2173.02, the definiteness of claim language must not be analyzed in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Likewise, the Federal Circuit has said:

Determining whether a claim is definite requires an analysis of “whether one skilled in the art would understand the bounds of the claim when read in light of the specification... If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.” *Personalized Media Communications v. International Trade Comm’n*, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998)(citing *Miles Lab., Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993)).

The Applicants believe that a person of ordinary skill in the art would understand the meaning of the term “biologically active agent” especially when it is read in light of the specification.

The Examiner asks if the term “biologically active agent” can include poisons or biochemical intermediates. (Office Action p. 7). The Applicants are unsure of what is meant by “poisons” or biochemical intermediates,” but the Applicants note that the specification at p. 15 teaches that the

biologically active compounds include, for example, anticancer agents, antiviral agents, and antibiotic agents. Certainly, many anticancer agents are known to be toxic.

During the telephonic interview, the Examiner explained that he believed that the compounds excluded by the claims were not biologically active. As explained during the interview, the excluded compounds are biologically active. Consequently, the proviso does not make the claims indefinite.

Therefore, the Applicants respectfully submit that claims 1-3, 7, 9-18, 20-46, 48-53, 150-157, 165-166, and 171-173 are definite and request removal of the rejection.

B. Claims 1-18, 20-46, 48-57, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

This rejection is respectfully traversed.

The Examiner finds the term “prodrug” to be indefinite. The Examiner states:

Applicants’ “prodrugs” are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a “prodrug.” Office Action p. 8

The Examiner notes that the Applicants have pointed out that they do claim prodrugs of formula (I). However, the Examiner finds the Applicants’ other arguments unpersuasive for three reasons.

These are:

Firstly, the passage uses open language “included but not limited to”. Secondly, the passage says that “standard prodrugs” are intended. Yet, Wolff (Burger’s Medicinal Chemistry) in section 9.1 makes clear that the design of prodrugs is an empirical exercise and no standard recipe exists, “may then be possible to identify the means by which the difficulties can be overcome”. Thirdly, we know what the concept of prodrug entails. What we do not know is what specific compounds the Applicants claim. Office Action pp. 8-9

The Applicants respectfully note that there is nothing wrong with the use of “open language” such as “include but are not limited to” in the specification. The key is whether “the claim apprises one of ordinary skill in the art of its scope.” M.P.E.P. § 2173.02. The Applicants assert that a person of ordinary skill in the art can determine what is or what is not a prodrug of the present invention. As Dr. Erion explains in his Declaration, “a person of ordinary skill in the art can readily determine what is or

what is not a prodrug of the current invention. The tests for making such determinations are routine and well-known in the art.” (Erion Decl. ¶ 4).

The Applicants respectfully assert that no standard recipe for “prodrugs” is required in order that the claims be definite. The specification describes the preparation of prodrugs of this invention. (See pp. 89-95 and Examples 12 and 13, pp. 113-114). Furthermore, prodrug technology is well understood in the art. Dr. Erion explains this further in his declaration saying:

The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 1999. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. (Erion Decl. ¶ 5).

As Dr. Erion has said in his declaration, a person of ordinary skill in the art would have no trouble understanding what is meant by the term “prodrug” as used in the claims of this invention. (Erion Decl. ¶¶ 8-9)

Indeed the term “prodrug” is commonly used in patent claims. A recent search of patents issued from 1976 to the present revealed that 343 patents used the term “prodrugs thereof” in the claims.

The Examiner continues to object to the use of a functional definition, in spite of case law to the contrary. As stated in MPEP § 2173.05(g), there is nothing inherently wrong with defining some part of an invention through functional terms. In fact the use of functional language has explicitly been approved by the Court of Appeals. When discussing functional language in *Swinehart*, the Court said:

In our view, there is nothing intrinsically wrong with the use of such a technique in drafting patent claims. Indeed, we have even recognized in the past the practical *necessity* for the use of functional language. *In re Swinehart and Sfiligoj*, 169 U.S.P.Q. 226, 228 (C.C.P.A. 1971).

Furthermore, MPEP § 2173.01 states:

Applicants may use functional language, alternative expressions, negative limitations, or any style of expression or format of claims which makes clear the boundaries of the subject matter for which the protection is sought. As noted in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought.

For example, *In re Barr*, the U.S. Court of Customs and Patent Appeals approved the use of functional language in defining the term “incapable of forming a dye with said oxidized developing agent.” See *In re Barr*, 170 U.S.P.Q. 330, 337 (C.C.P.A. 1971). The Court went on to say that:

In summary, we hold that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in “functional” terms, and that those “functional” terms may be “negative.” The real issue in any such case is not whether the recital is “functional” or “negative,” but whether the recital sets definite boundaries on the patent protection sought - that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112. *Id.*

Furthermore, a “limited use of terms of effect or result, which accurately define the essential qualities of a product to one skilled in the art, may in some instances be permissible and even desirable.” *In re Fuetterer*, 138 USPQ 217, 222 (C.C.P.A. 1963)(quoting *General Electric Co. v. Wabash Appliance Corp.*, 37 USPQ 466, 469 (U.S. 1938)).

The present situation is similar to the *In re Fuetterer* case. In that case, the examiner and the Board rejected certain composition claims as indefinite, ambiguous, unduly broad, and functional, in part because the term “inorganic salts” was defined in a functional way. *Id.* at 218-219. The examiner stated that:

“Inorganic salt” reads on literally thousands of materials, many of which would *not be operative* for applicant’s purpose. For example, some salts *could* readily react with other ingredients in the composition while other salts *could* be corrosive or destructive of the rubber. This recitation is functional since it merely describes how the salt functions as the surface of the tire wears away. *Id.* at 220.

First, the Court found that use of functional language was proper. *Id.* at 222. Then the Court went on to say that the claims were not unduly broad. *Id.* at 223. The Court stated:

in the words of the *second* paragraph of section 112, “applicant regards as his invention” the combination with his other tread ingredients of *any* inorganic salt *capable* of “maintaining the carbohydrate, the protein, or mixture thereof, in colloidal suspension* * *.” It is exactly this combination which appellant has particularly pointed out and *distinctly claimed* in compliance with the *second* paragraph of section 112...Appellant’s invention is the *combination* claimed and not the discovery that certain inorganic salts have colloidal suspending properties. We see nothing in the patent law which requires appellant to discover

which of all those salts have such properties and which will function in combination. *Id.*

The Court went on to point out that there was no “undue burden” caused by the functional language of the claims:

The Patent Office would require him to do research on the “literally thousands” of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented and is not claiming colloidal suspending agents but tire stock composed of a combination of rubber and other ingredients. *Id.*

Although not directly on point, since the claim in *Fuetterer* was a combination claim, the C.C.P.A. held that the same reasoning applies to elements in claims for compounds. *See In re Barr*, 170 U.S.P.Q. at 336 (stating that although *Fuetterer* was not directly on point “we feel that its rationale, if not its holding, is controlling here.”).

As in *Fuetterer*, it would be an undue burden on the Applicant to list each and every suitable prodrug. The desirability of functional language in these claims is clear.

As stated in *Barr*, the real issue is whether the Applicants have set definite boundaries on the patent protection sought. A person of ordinary skill in the art knows what a prodrug is. A person of ordinary skill in the art would also understand what the boundaries of the invention are, particularly when the claims are viewed in light of the specification. According to MPEP § 2173.02, when “reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claims as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph.” Accordingly, there is nothing wrong with defining the term “prodrug” in a functional manner. Nothing requires that the Applicants list each and every suitable prodrug. All that is required is that one of ordinary skill in the art can determine the scope of the claims. (The Applicants enclose copies of the above cited cases for the Examiner’s convenience.)

As explained by Dr. Erion in his declaration, a person of ordinary skill in the art can easily determine what is or what is not a prodrug of this invention, such tests are routine, and no undue experimentation is required. (Erion Decl. ¶¶ 4-5, and 9). In addition, Dr. Erion explains that the preparation of prodrugs is routine. (Erion Decl. ¶ 8). In the telephonic interview, the Examiner indicated

that he would give favorable consideration to such a declaration from Dr. Erion. In view of the above arguments and the declaration, the Applicants submit that a person of ordinary skill in the art would not find the use of the term "prodrug" to be indefinite.

Therefore, the Applicants respectfully submit that claims 1-18, 20-46, 48-57, 150-157, 165-166 and 171-173 are definite and request withdrawal of the rejection.

C. Claim 150 remains rejected as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

This rejection is respectfully traversed.

The Examiner says:

Claim 150 provides for transforming "a compound drug having a $-\text{PO}_3^{2-}$...", but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. All the word "transforming" does is delineate which molecules are starting materials and which are products. What chemical reactions are being claimed? Office Action p. 9

The Applicants again note that this is a process claim that contains the step of transforming a drug having a $-\text{PO}_3^{2-}$ or $-\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$ moiety into a compound of formula I.

According to MPEP § 2173.02:

Definiteness of claim language must be analyzed, not in a vacuum, but in light of

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Indeed, it is well established that "claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their 'broadest reasonable interpretation.'" *In re Okuzawa*, 537 F.2d 545, 548, 190 USPQ 464, 466 (C.C.P.A. 1976).

Here, the specification clearly provides guidance to a person of ordinary skill in the art. For example, the specification describes the phosphorylation of an alcohol under Mitsunobu reaction conditions. (p. 94). In the specification starting on p. 103, there are examples of prodrug compounds and general procedures for their preparation. The general procedure for phosphoramidate prodrugs begins with Example 1 and the general procedure for formation of nucleotide prodrugs begins with Example 4 on page 107. A person of skill in the art could use the methods disclosed in the specification to “transform” drugs having - PO_3^{2-} or - $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$ moieties into compounds of formula I.

In addition, the Applicants need not explain what is known to a person of ordinary skill in the art. According to MPEP § 2173.02, the claim language must be viewed in light of the interpretation that one of ordinary skill in the art would give to it. Since patents are written for persons of skill in the art of a particular field, patents need not contain subject matter that is known to persons of skill in the art. *See S3 Inc. v. nVidia Corp.*, 59 U.S.P.Q. 1745, 1748 (Fed. Cir. 2001).

A person of ordinary skill in the art would not find claim 150 to be indefinite, particularly in view of the specification and their own knowledge of the art. Therefore, the Applicants respectfully submit that claim 150 is definite and request withdrawal of the rejection.

D. Claims 155-157 remain rejected and claims 166 is newly rejected as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

This rejection is respectfully traversed.

The Examiner finds the term “oxidizing agent” to be indefinite. The Examiner points to two definitions of “oxidizing agent” and then says, “What are the structures of the reagents, whose use the Applicants claim?” (Office Action p. 10) The Examiner suggests listing the intended “oxidizing agents” on lines 16-18, p. 93.

The Examiner acknowledges the Applicants argument that the oxidizing agent is intended to oxidize the phosphorus atom to the +5 oxidation state, but the Examiner finds the argument unpersuasive. The Examiner says:

Attempting to define structure by function is not proper when the structures can be clearly expressed in terms that are more precise. It is not sufficient to define a chemical structure solely by a single chemical property. Office Action p. 10-11

The term "oxidizing agent" is given a functional definition in that it must be capable of transforming the phosphoramidite into a compound of formula I. As explained above, according to MPEP § 2173.05(g), there is nothing inherently wrong with defining some part of an invention through functional terms. In fact the use of functional language has explicitly been approved by the Court of Appeals.

As discussed in Section II.B. above, *In re Barr*, the U.S. Court of Customs and Patent Appeals approved the use of functional language in defining the term "incapable of forming a dye with said oxidized developing agent." See *In re Barr*, 170 U.S.P.Q. 330, 337 (C.C.P.A. 1971). The Court went on to say that:

In summary, we hold that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in "functional" terms, and that those "functional" terms may be "negative." The real issue in any such case is not whether the recital is "functional" or "negative," but whether the recital sets definite boundaries on the patent protection sought - that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112. *Id.*

As in *Barr*, a person of ordinary skill in the art would not have difficulty determining what the claims do or do not read on. The claim clearly encompasses oxidizing agents that are capable of transforming the phosphoramidite into a compound of formula I. Consequently, the functional language is not indefinite. In addition, as in *Fuetterer*, the use of functional language in this situation is desirable in comparison to listing every possible oxidizing agent. Therefore, the Applicants respectfully submit that claims 155-157 and 166 are definite and request withdrawal of the rejection.

III. THE 35 USC § 112, FIRST PARAGRAPH REJECTIONS

- A. **Claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected for failing to meet the written description requirement.**

This rejection is respectfully traversed.

The Examiner states:

The phrase in lines 16-17, page 128, "M is selected from...but is not an FB Pase inhibitor" lacks written description. Applicants' claims are drawn to any radical derived from a molecule with a certain functional group and

with a general biological property. What are the structures of these molecules? Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-157, 165, 166, and 171-173. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. Applicants' dependant claims, listing the specific diseases treated, do not clarify what chemical radicals are intended here. Office Action p. 11

The Examiner notes that Applicants have correctly argued that only a portion of claim 1 is claimed in functional terms and that some structural guidance is provided to the identity of M, "namely that when it is attached to a phosphorus atom, the resulting molecule be biologically active." (Office Action p. 12). The Examiner also notes the Applicants argument using the new *Written Description Guidelines*. (Office Action p. 12). After quoting from MPEP § 2163, the Examiner says that "radical M is an essential feature." (Office Action p. 13). The Examiner then says:

The question then, is, would the skilled medicinal chemist understand from the phrase in question, what radicals M were intended. The discussion above concerning the indefiniteness of this phrase means that they would not. Applicants' exclusions of alkyl amines from the list of claimed M groups means that they do not understand the phrase. Office Action p. 13

In the telephonic interview, the Examiner agreed that if the indefiniteness rejection is removed, the written description rejection would also be removed as to these claims. In light of the argument above, the Applicants believe that these claims are definite and also satisfy the written description requirement.

Therefore, the Applicants respectfully submit that claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-157, 165-166 and 171-173 meet the written description requirement and request withdrawal of the rejection.

B. Claims 1-18, 20-46, 48-57, 150-157, and 165 remain rejected and claims 166 and 171-173 are newly rejected as lacking enablement.

This rejection is respectfully traversed.

The Examiner states:

Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compounds. Since the structures of these "prodrugs" are uncertain, direction for their preparation must be even more unclear [?]. Office Action p. 13

The Examiner acknowledges the Applicants' argument that the preparation of prodrugs is standard in the art, but finds it unpersuasive for four reasons.

Firstly, the specification provides no structural guidance and defines "prodrug" in purely functional terms. We know what the concept of prodrug entails. What we do not know is what specific compounds Applicants claim. Secondly, none of the citations is of record or accessible to the Examiner. Thirdly, none of the references teaches how to make the prodrugs of Applicants compounds or even of compounds closely related by structure to Applicants'. Fourthly, finding a prodrug is a largely empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Office Action pp. 13-14

The Examiner believes that in order for a compound to be a prodrug it must meet three tests. These are 1) the compound is biologically inactive, 2) it must be metabolized to a second substance in human and at a rate and to an extent to produce a physiologically meaningful concentration, and 3) the second substance must be biologically active. (Office Action p. 14). The Examiner believes that in order to determine if a compound meets the "three criteria in a clinical trial setting passes the threshold of undue experimentation." (Office Action p. 14). The Examiner goes on to say:

Wolff (Burger's Medicinal Chemistry in section 9.1 outlines the research program that must be undertaken to prepare a prodrugs including collaboration between the skilled medicinal chemists and metabolism specialists. Banker (Modern Pharmaceuticals) says on page 451, first paragraph that "preparation of prodrugs is becoming common practice", implying that it is not routine as of 1996. Banker (Modern Pharmaceuticals) says on page 596, third paragraph that "extensive development must be undertaken to find the correct chemical modification". Clearly an invitation to open-ended and potentially inconclusive research. Office Action p. 14

First, the Applicants note that according to the above definition and what is known in the art, "in some cases, the prodrug is biologically active usually less than the drug itself, and serves to improve efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, etc." Therefore, the first test suggested by the Examiner is not a requirement per se for prodrugs. However, determining whether a compound meets any of the three criteria set out by the Examiner requires only routine testing.

As explained above in Section II.B., MPEP § 2173.05(g) explains that there is nothing inherently wrong with defining some part of an invention through functional terms. In fact the use of functional

language has explicitly been approved by the Court of Appeals. When discussing functional language in *Swinehart*, the Court said:

In our view, there is nothing intrinsically wrong with the use of such a technique in drafting patent claims. Indeed, we have even recognized in the past the practical *necessity* for the use of functional language. *In re Swinehart and Sfiligoj*, 169 U.S.P.Q. 226, 228 (C.C.P.A. 1971).

The key is whether “the claim apprises one of ordinary skill in the art of its scope.” M.P.E.P. § 2173.02. As Dr. Erion explains in his Declaration, “a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for making such determinations are routine and well-known in the art.” (Erion Decl. ¶ 4). Furthermore, prodrug technology is well understood in the art. Dr. Erion explains this further in his declaration saying:

The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 1999. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. (Erion Decl. ¶ 5).

In fact, the Applicants have provided structural guidance as to what is meant by the term “prodrug.” As explained by Dr. Erion

As defined at p. 15 of the specification a prodrug is a compound that undergoes a chemical modification to form a biologically active molecule or a precursor to the biologically active drug. There are many commonly known prodrugs. For example, a compound may have a free hydroxyl group on it. A common prodrug of a hydroxyl is an ester. Esters are often quickly broken down within the body to produce the compound with the free hydroxyl. In this example, the ester is the prodrug. In general, each functional group, *e.g.* hydroxyl, thiol, amine, carboxylic acid, has a set of well described prodrugs that have proven useful for masking the functional group in a manner that enables improved oral bioavailability, improved pharmacokinetics, improved distribution, or other properties readily observable during testing in animals and man. (Erion Decl. ¶ 4).

In addition, the specification gives examples for the preparation of prodrugs of this invention. (See pp. 89-95 and Examples 12 and 13, pp. 113-114). According to MPEP § 2164.01(b), “As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied.” Dr. Erion explains that “a person of ordinary skill in the art could routinely prepare

prodrugs of the invention particularly in view of the general procedures for prodrug preparation given at pp. 89-95 of the specification and by the definition of the term “prodrug” at p. 15 of the specification.” (Erion Decl. ¶ 8).

The Examiner refers to certain citations not being of record. (Office Action pp. 13-14). Apparently, the Examiner is referring to two textbooks cited in the previous response. The Applicants were merely attempting to demonstrate that “prodrug” technology has been well-known in the art for years. Typically textbooks are written on fully-developed fields and not on cutting edge technology.

There is no requirement that any textbook contain a recipe for making “prodrugs” of the Applicants’ invention. The specification describes the preparation of prodrugs of this invention. (See pp. 89-95 and Examples 12 and 13, pp. 113-114). As Dr. Erion has explained “a person of ordinary skill in the art could routinely prepare prodrugs of the invention particularly in view of the general procedures for prodrug preparation given at pp. 89-95 of the specification and by the definition of the term “prodrug” at p. 15 of the specification.” (Erion Decl. ¶ 8).

Contrary to the Examiner’s position, finding prodrugs in not a largely empirical exercise filled with experimental uncertainty. Dr. Erion explains this further in his declaration saying:

The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 1999. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. (Erion Decl. ¶ 5).

As Dr. Erion has said in his declaration, a person of ordinary skill in the art would have no trouble understanding what is meant by the term “prodrug” as used in the claims of this invention. (Erion Decl. ¶¶ 8-9).

The Examiner refers to *Banker* and interprets the phrase “preparation of prodrugs is becoming a common practice” to mean that it is not routine of 1996. (Office Action p. 14). First, the Applicants are not clear that this is the proper interpretation of the phrase from *Banker*. Second, 1996 is not the filing date of this Application. State of the art in 1996 is not necessarily state of the art in 1999, particularly when it comes to textbooks that are written well in advance of publication.

The Examiner also points to the research program outlined in *Burger* and to the phrase “extensive development must be undertaken to find the correct chemical modification” in *Banker* as “an invitation to open-ended and potentially inconclusive research.” (Office Action p. 14). Again, the Applicants respectfully disagree with the Examiner’s interpretation of these textbook sections. In any event, the Applicants are not clear as to why the Examiner finds these textbooks persuasive. The enablement requirement does not require that there be no experimentation. As stated in M.P.E.P. § 2164.01:

The fact that some experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation... The test of enablement is not whether any experimentation is necessary, but whether if experimentation is necessary, it is undue. M.P.E.P. § 2164.01 (internal citations omitted)

In fact, Dr. Erion has explained that a person of ordinary skill in the art can routinely prepare the prodrugs of this invention without undue experimentation. (Erion Decl. ¶ 8) It should be noted that the Court has cautioned against the Examiner substituting his opinion for that of one skilled in the art. For example when speaking to an obviousness rejection, the Court said:

We do not think it was the intent of section 103 that either the examiner, the board, or this court should substitute their own speculations for the factual knowledge of those skilled in the art. Where, as here, an affidavit states facts which are relevant to the ultimate determination of the legal issue arising under 103, we think it must be given careful evaluation and properly weighed to determine whether it factually rebuts the bases upon which the examiner has predicated his findings of obviousness. *In re Katzschmann*, 146 U.S.P.Q. 66, 68 (C.C.P.A. 1965).

As explained by Dr. Erion in his declaration, a person of ordinary skill in the art can easily determine what is or what is not a prodrug of this invention, such tests are routine, and no undue experimentation is required. (Erion Decl. ¶¶ 4-5, and 9). In addition, Dr. Erion explains that the preparation of prodrugs is routine. (Erion Decl. ¶ 8). In the telephonic interview, the Examiner indicated that he would give favorable consideration to such a declaration from Dr. Erion. In view of the above arguments and the declaration, the Applicants submit that a person of ordinary skill in the art would find that the claims are enabled.

Therefore, the Applicants respectfully request withdrawal of the rejection that claims 1-18, 20-46, 48-57, 150-157, 165-166 and 171-173 are not enabled.

IV. THE 35 USC § 101 REJECTION

Claim 150 remains rejected under 35 USC § 101 because the Examiner says it is an improper process claim. This rejection is respectfully traversed.

The Examiner says that the Applicants appear to agree that there are no steps are indicated in the claimed process. The Examiner goes on to say:

While the process may consist of a single step, how is the enablement and written support for the claim to be determined if we do not know of what the process consists? How is the public to understand the metes and bounds of the claim? Office Action p. 10

The Applicants do not agree that there are no steps indicated in the claimed method. Claim 150 is directed toward a method of making a compound of formula I comprising the step of transforming a drug having a $-PO_3^{2-}$ or $-P(O)(NHR^6)O^-$ moiety into a compound of formula I. As pointed out in the previous response, this is a process claim and not a use claim.

There is no requirement that process claims contain multiple steps. The Applicants believe that the claim is a proper process claim and that the 35 USC § 101 rejection is improper. 35 USC § 101 clearly allows the patenting of processes, machines, manufactures, and compositions of matter. Claim 150 is clearly a process claim. Therefore, the Applicants respectfully request withdrawal of the rejection that claim 150 is an improper process claim under 35 USC § 101.

CONCLUSION

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted,

Date: 4/10/03

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MARKED UP COPY OF THE AMENDED SPECIFICATION

Page 14, line 4

The terms "alkylthio-" and "alk[yl]thio-" refer to the groups alkyl-S-.

Page 20, lines 16-21

The term "enhanced oral bioavailability" refers to an increase of at least 50% of the absorption of the dose of the parent drug or prodrug (not of this invention) from the gastrointestinal tract. More preferably it is at least 100%. Measurement of oral bioavailability usually refers to measurements of the prodrug, drug, or drug metabolite in blood, tissues, or urine following oral administration compared to measurements following systemic administration.

Page 25, line 30- page 26, line 12

Compounds of the formula $M-P(O)(NHR^6)O^-$ are useful compounds for binding to nucleotide binding sites, such as AMP-binding sites, and certain sites known to recognize negatively charged compounds, e.g. carboxylic and phosphinic acids. Enzymes that catalyze the addition of water to a carbonyl compound, specifically a peptide carbonyl, an ester, a ketone or an aldehyde, are of particular interest since these enzymes recognized compounds that are tetrahedral and contain a negatively charged oxygen. An example is the zinc metalloproteinase class of enzymes which add water across a peptide carbonyl using a zinc-assisted catalytic mechanism. These enzymes are inhibited by phosphoramidates, e.g. NEP 24.11 is inhibited by the natural product Phosphoramidon. The prodrug strategy can provide a useful means for delivery of these compounds orally, or delivery of certain compounds to the liver in order to achieve greater efficacy or a greater therapeutic window. Enzyme[s] inhibitors that may be suitable for delivery as prodrugs include certain phosphoramidates that inhibit NEP24.11, collagenase, stromolysin, gelatinase, ACE, endothelin converting enzyme, and metalloproteinases involved in matrix remodeling such as occurs in Rheumatoid arthritis and osteoarthritis and in the heart following an acute myocardial infarction, and tumor metastasis.

Page 35, lines 7-13

Another common toxicity associated with phosphonic acid drugs is gastrointestinal toxicity via in some cases GI erosions. Prodrugs of the current invention can decrease GI toxicities, especially toxicities produced by direct action of the drug on the GI tract after oral administration. Similar to the kidney, gut epithelial cells have organic anion transporters which can result in high intracellular drug levels and cytotoxicity. Since the negatively charged phosph(on)ate is not revealed until after absorption and cleavage in the liver, prodrugs of this invention reduce gut toxicity.

Page 96, lines 7-29

1,3-Dihydroxy compounds can be synthesized by several well known methods in literature. Aryl Grignard additions to 1-hydroxy propan-3-al give 1-aryl-substituted propan-1,3-diols. This

method will enable conversion of various substituted aryl halides to 1-arylsubstituted-1,3-propane diols (Coppi, *et al.*, *J. Org. Chem.*, **1988**, *53*, 911). Aryl halides can also be used to synthesize 1-substituted propanediols by Heck coupling of 1,3-diox-4-ene followed by reduction and hydrolysis (Sakamoto, *et al.*, *Tetrahedron Lett.*, **1992**, *33*, 6845). Substituted 1,3-diols can be generated enantioselective reduction of vinyl ketone and hydroboration or by kinetic resolution of allylic alcohol. Variety of aromatic aldehydes can be converted to 1-substituted-1,3-diols by vinyl Grignard addition followed by hydroboration. Substituted aromatic aldehydes are also utilized by lithium-t-butylacetate addition followed by ester reduction (Turner, *J. Org. Chem.*, **1990**, *55* 4744). In another method, commercially available cinnamyl alcohols can be converted to epoxy alcohols under catalytic asymmetric epoxidation conditions. These epoxy alcohols are reduced by Red-Al to result in enantiomerically pure 1,3-diols (Gao, *et al.*, *J. Org. Chem.*, **1980**, *53*, 4081). Alternatively, enantiomerically pure 1,3-diols can be obtained by chiral borane reduction of hydroxyethyl aryl ketone derivatives (Ramachandran, *et al.*, *Tetrahedron Lett.*, **1997**, *38* 761). Pyridyl, quinoline, isoquinoline propan-3-ol derivatives can be oxygenated to 1-substituted-1,3-diol by N-oxide formation followed by rearrangement in acetic anhydride conditions (Yamamoto, *et al.*, *Tetrahedron*, **1981**, *37*, 1871). Aldol condensation is another well described method for synthesis of the 1,3-oxygenated functionality (Mukaiyama, *Org. React.*, **1982**, *28*, 203). Chiral substituted diols can also be made by enantioselective reduction of carbonyl compounds, by chiral aldol condensation or by enzyme promoted kinetic resolution.

Page 110, lines 25-27

Prodrugs of 2-substituted-1,3-amino alcohols or 2-substituted-1,3-diamines are synthesized by following coupling procedures as described in example 1 or example 2 (step A and B) or example 3 (step B) or example 4 depending on the parent compound.

Page 122, lines 3-8

Methods: The choice of cell line is dictated by the known toxicity profile of the parent compound. If the toxicity profile of a parent compound is unknown, a panel of different cultured cell lines can be tested. Cells are exposed to a range of prodrug and parent compound concentrations for hours to days. Viability is[the] measured by Trypan blue exclusion, enzyme marker leakage, incorporation of labeled thymidine into DNA or other standard method.

Page 124, lines 19-26

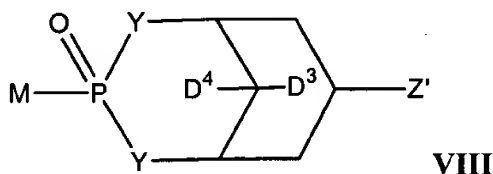
Methods: Rats are treated with dexamethasone (50 mg/kg, intraperitoneally) for 4 days as described (Brain EGC et al 1998, *Br. J. Cancer* *7*: 1768). Other CYP-inducing agents such as Phenobarbital or rifampicin may also be used. The induced animals are then administered prodrug orally or systemically and serially sacrificed at various time points. Livers are removed and homogenized in perchloric acid (10%). Following clarification by centrifugation and neutralization, $\text{MPO}_2\text{-(NHR}^6\text{)}$ and/or its metabolites in the homogenates are quantified by standard HPLC methods. A similar study is conducted in uninduced animals.

MARKED UP COPY OF AMENDED CLAIMS

31. (Once amended) The compounds of claim 1 wherein V is -H, and Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC(O)R}^3$, and $-\text{CHR}^2\text{OCO}_2\text{R}^3$.

35. (Once amended) The compounds of claim 22 wherein W and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, $[\text{R}^3]$ aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

173. (Once amended) The compounds of claim 1 that are of formula VIII:



wherein:

Z' is selected from the group consisting of $-\text{OH}$, $-\text{OCO}_2\text{R}^3$, $-\text{OC(O)R}^3$, and $-\text{OC(O)SR}^3$;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

D³ is -H;

D⁴ is selected from the group consisting of -H, alkyl, -OH, -OR² and -OC(O)R³.

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, $\text{P}_3\text{O}_9^{4-}$ or $\text{P(O)(NHR}^6\text{)O}^-$ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not $-\text{NH}(\text{lower alkyl})$, $-\text{N}(\text{lower alkyl})_2$, $-\text{NH}(\text{lower alkylhalide})$, $-\text{N}(\text{lower alkylhalide})_2$, or $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$; and

2) R⁶ is not lower alkylhalide;

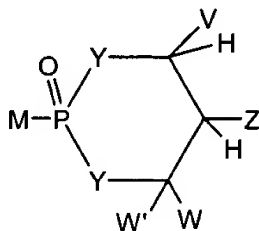
and pharmaceutically acceptable prodrugs and salts thereof.



Pending Claims in the 0013.CIP1

Patent
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1. (Once amended) A compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p\text{-OR}^{12}$, and $-(\text{CH}_2)_p\text{-SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxy-carbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is $-\text{NR}^6$ -;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, $\text{P}_3\text{O}_9^{4-}$ or $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not $-\text{NH}(\text{lower alkyl})$, $-\text{N}(\text{lower alkyl})_2$, $-\text{NH}(\text{lower alkylhalide})$, $-\text{N}(\text{lower alkylhalide})_2$, or $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$; and
 - 2) R^6 is not lower alkylhalide;
- and pharmaceutically acceptable prodrugs and salts thereof.

2. (Once amended) The compounds of claim 1 wherein $\text{MP}(\text{O})(\text{NHR}^6)\text{O}^-$, MPO_3^{2-} , $\text{MP}_2\text{O}_6^{3-}$, or $\text{MP}_3\text{O}_9^{4-}$ is selected from the group consisting of an antiviral, anticancer, antihyperlipidemic, antifibrotic, and antiparasitic agent.

3. (Once amended) The compound of claim 1 wherein $\text{MP}(\text{O})(\text{NHR}^6)\text{O}^-$, MPO_3^{2-} , $\text{MP}_2\text{O}_6^{3-}$, or $\text{MP}_3\text{O}_9^{4-}$ is selected from the group consisting of metalloprotease inhibitor and TS inhibitor.

4. The compounds of claim 2 wherein MH is selected from the group consisting of LdC, LdT, araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L-FddC, L-d4C, L-Fd4C, 3TC, ribavirin, penciclovir, 5-fluoro-2'-deoxyuridine, FIAU, FIAC, BHCG, 2'R,5'S(-)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine, (-)-b-L-2',3'-dideoxycytidine, (-)-b-L-2',3'-dideoxy-5-fluorocytidine, FMAU, BvaraU, E-5-(2-bromovinyl)-2'-deoxyuridine, Cobucavir, TFT, 5-propynyl-1-arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'-deoxyguanosine, Cytallene, Oxetanocin A, Oxetanocin G, Cyclobut A, Cyclobut G, fluorodeoxyuridine, dFdC, araC, bromodeoxyuridine, IDU, CdA, F-araA, 5-FdUMP, Coformycin, and 2'-deoxycoformycin.

5. The compounds of claim 2 wherein MH is selected from the group consisting of ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, and cytallene.

6. The compounds of claim 1 wherein MPO_3^{2-} is selected from the group consisting of PMEA, PMEDAP, HPMPC, HPMPA, FPMMPA, and PMPA.

7. The compounds of claim 3 wherein M is attached to the phosphorus in formula I via an oxygen atom that is in a hydroxyl group on an acyclic sugar group.

8. The compounds of claim 7 wherein MH is selected from the group consisting of ACV, GCV, 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine, and (R)-9-(3,4-dihydroxybutyl)guanine.

9. The compounds of claim 1 wherein M is attached to the phosphorus in formula I via a carbon atom.

10. The compounds of claim 9 wherein $M-PO_3^{2-}$ is selected from the group consisting of phosphonoformic acid, and phosphonoacetic acid.

11. The compounds of claim 1 wherein $MP(O)(NH R^6)O^-$, MPO_3^{2-} , $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ is useful for the treatment of diseases of the liver or metabolic diseases where the liver is responsible for the overproduction of a biochemical end product.

12. The compounds of claim 11 wherein said disease of the liver is selected from the group consisting of hepatitis, cancer, fibrosis, malaria, gallstones, and chronic cholecystolithiasis.

13. The compounds of claim 12 wherein MPO_3^{2-} , $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ is an antiviral or anticancer agent.

14. The compounds of claim 11 wherein said metabolic disease is selected from the group consisting of diabetes, atherosclerosis, and obesity.

15. The compounds of claim 11 wherein said biochemical end product is selected from the group consisting of glucose, cholesterol, fatty acids, and triglycerides.

16. The compounds of claim 15 wherein MPO_3^{2-} or $MP(O)(NHR^6)O^-$ is an AMP activated protein kinase activator.

17. The compounds of claim 1 wherein Y is -O- located adjacent to the W' and W groups.

18. The compounds of claim 1 wherein Y is -O- located adjacent to the V group.

20. The compounds of claim 1 wherein
V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus.

21. The compounds of claim 20 wherein V is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl; or

together V and W are connected via an additional 3 carbon atoms to form a cyclic substituted group containing 6 carbon atoms and mono-substituted with a substituent selected from the group consisting of hydroxyl, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy attached to one of said additional carbon atoms that is three atoms from an Y attached to the phosphorus.

22. The compounds of claim 21 wherein V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

23. The compounds of claim 22 wherein Z, W, and W' are H; and R⁶ is selected from the group consisting of -H, and lower alkyl.

24. The compounds of claim 23 wherein V is selected from the group consisting of aryl and substituted aryl.

25. The compounds of claim 24 wherein V is selected from the group consisting of phenyl, and substituted phenyl.

26. The compounds of claim 25 wherein V is selected from the group consisting of 3,5-dichlorophenyl, 3-bromo-4-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, and 3,5-difluorophenyl.

27. The compounds of claim 22 wherein V is selected from the group consisting of heteroaryl and substituted heteroaryl.

28. The compounds of claim 27 wherein V is 4-pyridyl.

29. The compounds of claim 21 wherein together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and mono-substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy attached to one of said additional carbon atoms that is three atoms from an Y attached to the phosphorus.

30. The compounds of claim 29 wherein together V and W form a cyclic group selected from the group consisting of $-\text{CH}_2\text{-CH(OH)-CH}_2-$, $-\text{CH}_2\text{CH(OCOR}^3\text{)-CH}_2-$, and $-\text{CH}_2\text{CH(OCO}_2\text{R}^3\text{)-CH}_2-$.

31. (Once amended) The compounds of claim 1 wherein V is -H, and Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC(O)R}^3$, and $-\text{CHR}^2\text{OCO}_2\text{R}^3$.

32. The compounds of claim 22 wherein Z is selected from the group consisting of $-\text{OR}^2$, $-\text{SR}^2$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-(\text{CH}_2)_p\text{-OR}^{12}$, and $-(\text{CH}_2)_p\text{-SR}^{12}$.

33. The compounds of claim 32 wherein Z is selected from the group consisting of $-\text{OR}^2$, $-\text{R}^2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-(\text{CH}_2)_p\text{-OR}^{12}$, and $-(\text{CH}_2)_p\text{-SR}^{12}$.

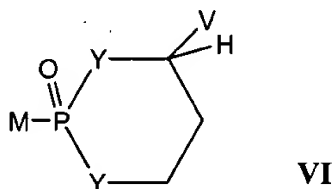
34. The compounds of claim 33 wherein Z is selected from the group consisting of $-\text{OR}^2$, -H, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, and $-\text{NHCOR}^2$.

35. The compounds of claim 22 wherein W and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

36. The compounds of claim 35 wherein W and W' are the same group.

37. The compounds of claim 36 wherein W and W' are H.

38. (Once amended) The compounds of claim 20 wherein said compound is of formula VI:



wherein

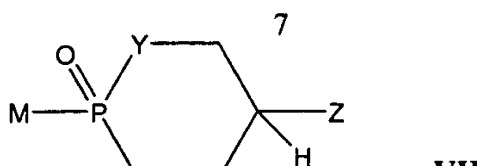
V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

39. The compounds of claim 38 wherein M is attached to phosphorus via an oxygen or carbon atom.

40. The compounds of claim 38 wherein V is selected from the group consisting of phenyl and substituted phenyl.

41. The compounds of claim 38 wherein V is selected from the group consisting of 3,5-dichlorophenyl, 3-bromo-4-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, and 4-pyridyl.

42. (Once amended) The compounds of claim 20 wherein said compound is of formula VII:



wherein

Z is selected from the group consisting of:

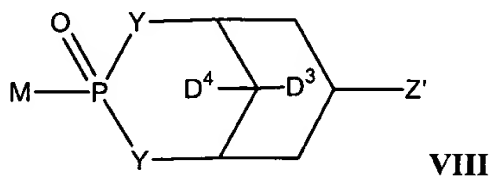
-CHR²OH, -CHR²OC(O)R³, -CHR²OC(S)R³, -CHR²OCO₂R³, -CHR²OC(O)SR³,
-CHR²OC(S)OR³, and -CH₂aryl.

43. The compounds of claim 42 wherein M is attached to the phosphorus via a carbon or oxygen atom.

44. The compounds of claim 43 wherein Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³, and -CHR²OCO₂R³.

45. The compounds of claim 44 wherein R² is -H.

46. (Once amended) The compounds of claim 20 wherein said compound is of formula VIII:



wherein

Z' is selected from the group consisting of -OH, -OC(O)R³, -OCO₂R³, and -OC(O)SR³;

D³ is -H;

D⁴ is selected from the group consisting of -H, alkyl, -OH, and -OC(O)R³.

48. (Once amended) The compounds of claim 32 wherein W and W' are H, V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and Z is selected from the group consisting of -H, OR², and -NHCOR².

49. The compounds of claim 48 wherein Z is -H, and M is attached to the phosphorus of formula I via an oxygen or carbon atom.

50. (Once amended) The compounds of claim 49 wherein V is selected from the group consisting of phenyl and substituted phenyl.

51. The compounds of claim 49 wherein V is an optionally substituted monocyclic heteroaryl containing at least one nitrogen atom.

52. The compounds of claim 49 wherein M is attached via an oxygen atom.

53. The compounds of claim 51 wherein V is 4-pyridyl.

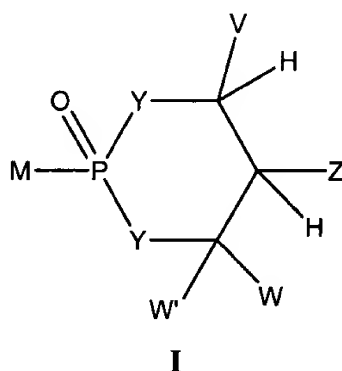
54. The compounds of claim 52 wherein MH is selected from the group consisting of LdC, LdT, araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L-FddC, L-d4C, L-Fd4C, 3TC, ribavirin, penciclovir, 5-fluoro-2'-deoxyuridine, FIAU, FIAC, BHCG, 2'R,5'S(-)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine, (-)-b-L-2',3'-dideoxycytidine, (-)-b-L-2',3'-dideoxy-5-fluorocytidine, FMAU, BvaraU, E-5-(2-bromovinyl)-2'-deoxyuridine, Cobucavir, TFT, 5-propynyl-1-arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'-deoxyguanosine, Cytallene, Oxetanocin A, Oxetanocin G, Cyclobut A, Cyclobut G, fluorodeoxyuridine, dFdC, araC, bromodeoxyuridine, IDU, CdA, F-ara-A, 5-FdUMP, coformycin, and 2'-deoxycoformycin.

55. The compounds of claim 52 wherein MH is selected from the group consisting of ACV, GCV, 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine, and (R)-9-(3,4-dihydroxybutyl)guanine.

56. The compounds of claim 49 wherein M is attached to the phosphorus via a carbon atom.

57. The compounds of claim 56 wherein V is selected from the group consisting of phenyl and 4-pyridyl and MH is selected from the group consisting of PMEA, PMEDAP, HPMPC, HPMMA, FPMMA, and PMPA.

150. (Once amended) A method of making a compound of Formula I comprising,
 a) transforming a drug having a $-\text{PO}_3^{2-}$ or $-\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$ moiety into a compound of formula I:



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkylthio, and aryloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxy-carbonyloxyalkyl, and lower acyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is $-\text{NR}^6$ -;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, $\text{P}_3\text{O}_9^{4-}$, or $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not $-\text{NH}(\text{lower alkyl})$, $-\text{N}(\text{lower alkyl})_2$, $-\text{NH}(\text{lower alkylhalide})$, $-\text{N}(\text{lower alkylhalide})_2$, or $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$; and
 - 2) R^6 is not lower alkylhalide;
- and pharmaceutically acceptable prodrugs and salts thereof.

151. (Once amended) The method of claim 150 further comprising,
- converting $M-PO_3^{2-}$ to a compound $M-P(O)L''_2$ wherein L'' is a halogen; and
 - reacting $M-P(O)L''_2$ with $HY-CH(V)CH(Z)-CW(W')-YH$.

152. The method of claim 151 wherein $HY-CH(V)CH(Z)-CW(W')-YH$ is chiral.

153. The method of claim 152 further comprising isolating a single diastereomer.

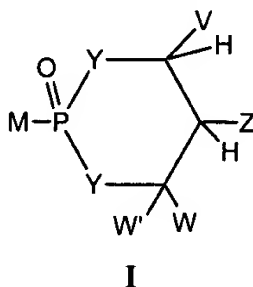
155. (Once amended) The method of claim 166 wherein $L-P(-YCH(V)CH(Z)-CW(W')Y-)$ is chiral.

156. The method of claim 155 wherein the chiral phosphoramidite is generated using a chiral amino alcohol.

157. The method of claim 155 wherein said oxidizing agent produces a single stereoisomer at the phosphorus.

165. (Once amended) The compounds of claim 1 wherein V and M are *cis* to one another on the phosphorus-containing ring of Formula I.

166. The method of making a compound of formula I:



comprising

- converting a hydroxyl or amino on M to a phosphoramidite by reaction with $L-P(-YCH(V)CH(Z)-CW(W')Y-)$ wherein L selected from the group consisting of NR^1_2 and halogen; and

b) transforming said phosphoramidite into a compound of formula I by reaction with an oxidizing agent;
wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

each R¹ is independently selected from the group consisting of alkyl, aryl, and aralkyl or together R¹ and R¹ form a cyclic group, optionally containing a heteroatom;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R⁶ is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxyalkoxyalkyl, and lower acyl;

R¹² is selected from the group consisting of -H, and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻, or P(O)(NHR⁶)O⁻ is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not -NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), -N(lower alkylhalide)₂, or -N(lower alkyl) (lower alkylhalide);
- 2) R⁶ is not lower alkylhalide; and
- 3) R¹ is not methyl.

171. The compounds of claim 1, wherein:

W and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³, -CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -OR², -SR², -CHR²N₃, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²)OH, -CH(C≡CR²)OH, -R², -NR²₂, -OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl, -(CH₂)_p-OR¹², and -(CH₂)_p-SR¹²; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

p is an integer 2 or 3;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

R^{12} is selected from the group consisting of -H and lower acyl;

one Y is -O- and the other Y is -NR⁶-;

M is selected from the group that attached to PO_3^{2-} , $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 1) M is not -NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), -N(lower alkylhalide)₂, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R^6 is not lower alkylhalide;
- and pharmaceutically acceptable prodrugs and salts thereof.

172. The compounds of claim 1, wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³, -CHR²OC(S)R³, -CHR²OC(S)OR³, -CHR²OC(O)SR³, -CHR²OCO₂R³, -CH₂aryl, -CH(aryl)OH, -CH(CH=CR²)OH, -CH(C≡CR²)OH, -SR², and -CH₂NHaryl; or

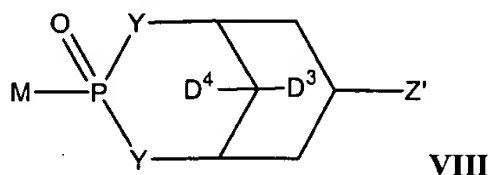
together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;
 R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxy-carbonyloxy alkyl and lower acyl;
 one Y is -O- and the other Y is -NR⁶-;
 M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;
 with the provisos that:

- 1) M is not -NH(lower alkyl), -N(lower alkyl)₂, -NH(lower alkylhalide), -N(lower alkylhalide)₂, or -N(lower alkyl) (lower alkylhalide); and
 - 2) R⁶ is not lower alkylhalide;
- and pharmaceutically acceptable prodrugs and salts thereof.

173.(Once amended) The compounds of claim 1 that are of formula VIII:



wherein:

Z' is selected from the group consisting of -OH, -OCO₂R³, -OC(O)R³, and -OC(O)SR³;
 R^2 is selected from the group consisting of R³ and -H;
 R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;
 R^6 is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxy-carbonyloxy alkyl and lower acyl;
 one Y is -O- and the other Y is -NR⁶-;
 D^3 is -H;
 D^4 is selected from the group consisting of -H, alkyl, -OH, -OR² and -OC(O)R³.
 M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, P₃O₉⁴⁻ or P(O)(NHR⁶)O⁻ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not -NH(lower alkyl) , -N(lower alkyl)_2 , $\text{-NH(lower alkylhalide)}$, $\text{-N(lower alkylhalide)}_2$, or $\text{-N(lower alkyl) (lower alkylhalide)}$; and

2) R^6 is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.